Sample of a Written Request for Proton-Pump Inhibitors
Used to Treat Gastroesophageal Reflux Disease (GERD)

This is a sample Written Request outlining the pediatric studies the Agency believes will provide a meaningful health benefit to the pediatric population for proton-pump inhibitors (PPI) used to treat Gastroesophageal Reflux Disease. An actual Written Request may differ from this sample depending upon the nature of the specific drug product and any other indications for which it is used. To receive a formal Written Request for pediatric studies under section 505A of the Federal Food, Drug, and Cosmetic Act for a particular PPI, please submit a proposed pediatric study request to the Division of Gastro-Intestinal and Coagulation Drug Products. The proposed pediatric study request should incorporate the material in this sample and include descriptions of any other studies necessary to provide a meaningful health benefit to pediatric populations. Please refer to the outline in the "Guidance For Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act," for additional information.

Application Number(s):
Sponsor:
Attention: Contact, Title
Address:

Dear Contact:

Reference is made to your Proposed Pediatric Study Request submitted on [*INSERT DATE*] for [*INSERT DRUG NAME*] to IND [*INSERT NUMBER*].

To obtain needed pediatric information on [*INSERT DRUG NAME*], the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the studies described below.

Background:

Proton-pump inhibitors are used widely in pediatric patients for the treatment of gastroesophageal reflux disease (GERD) or its manifestations, and medical publications recommend use of proton-pump inhibitors for this purpose. The Food and Drug Administration (FDA) is therefore issuing Written Requests for proton-pump inhibitors where the additional information would produce a public health benefit.

The template for Written Requests for proton-pump inhibitors used in the treatment of GERD covers the pediatric age range from birth through 16 years of age. The types of studies that are requested differ for each of four age groups encompassed by the Written Request. For further details on the four age groups see attachment.

As used in this written request, a *preterm infant* is an infant who has completed less than 38 complete weeks of gestation. A *term infant* is an infant that has completed 38-42 weeks gestation, and a *post-term infant* is an infant that has completed more than 42 weeks gestation. For preterm infants, *corrected age* is the sum of the gestational age and the age since birth. For example, a preterm infant born after 32 weeks gestation for which 12 weeks have elapsed since birth has a corrected age of 44 weeks. The *neonatal period* is the first 28 days since birth.

Type of Studies:

The course of gastroesophageal reflux disease (GERD) in adults is not sufficiently similar to the course of pathological gastroesophageal reflux in pediatric patients less than one year of age to permit extrapolation of the adult efficacy data to this pediatric age group. The effects of [*INSERT DRUG NAME*], both beneficial and adverse, may also differ in adults from those in patients less than one year of age. Therefore, to fulfill the conditions of this Written Request, efficacy studies must be performed in pediatric patients less than one year of age (see Studies 2 and 4).

Study 1: Pharmacokinetic (Pk), Pharmacodynamic (Pd), and Safety Study in Neonates and in Preterm Infants With a Corrected Age Less Than 44 Weeks

Inclusion criteria: To be included in this study, infants will (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery, (b) have evidence of obstructive apnea by pneumographic monitoring, (c) be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (d) either be term or post-term infants within the neonatal period, or be preterm infants with a corrected age of less than 44 weeks, and (e) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in the study.

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of [*INSERT DRUG NAME*]. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose PK, PD, and safety study of [*INSERT DRUG NAME*]. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete this part of the study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six of these (or other) patients who require tube placement or pH monitoring for clinical management not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Study 2: Efficacy and Safety Study in Neonates and in Preterm Infants with a Corrected Age of Less than 44 Weeks

Inclusion criteria: To be included in this study, patients must meet the same inclusion criteria specified above for Study 1.

Design: This will be a multicenter, treatment-withdrawal study of the efficacy and safety of [*INSERT DRUG NAME*] in which treatment withdrawal is randomized, double-blind, and placebo-controlled. The dosage(s) of [*INSERT DRUG NAME*] used in this study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 1 and as suggested by the results of other studies (e.g., literature studies of pediatric patients). Patients will be stratified by whether or not they are receiving methylxanthine (e.g., theophylline, caffeine) for treatment of central apnea and

by corrected age. Protocol design will also consider whether or not patients receive concomitant prokinetic agents (e.g., metoclopramide, erythromycin). The number of patients per treatment group required to complete the study is described in the Statistical Information section. Independent data review committees (e.g., for safety, efficacy, or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Run-in phase: All patients will receive [*INSERT DRUG NAME*] in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by [*INSERT DRUG NAME*] is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this part of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

Withdrawal phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of [*INSERT DRUG NAME*] or to receive matching placebo. Following randomization, patients will be monitored closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

Therapy for central apnea will be tracked. Individuals such as caregivers, who will be making observational assessments of apnea or bradycardia, will be trained appropriately in apnea/bradycardia monitoring procedures. Additionally, cardiorespiratory monitors used to assess apnea and bradycardia will be capable of recording and storing each patient's data for the duration of the study.

Study 3: Pharmacokinetic, Pharmacodynamic and Safety Study in Pediatric Patients 1 To 11 Months of Age

Inclusion criteria: To be included in this study, infants will (a) be hospitalized patients considered to be candidates for acid suppressive therapy because of a presumptive diagnosis of GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in the study.

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of [*INSERT DRUG NAME*]. Adequate justification for dose selection will be provided. Patients will be allocated to treatment groups in approximately equal proportions. At least 20 patients (i.e., at least 10 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated dose PK, PD, and safety study of [*INSERT DRUG NAME*] in pediatric patients. The study will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of [*INSERT DRUG NAME*]. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six of these (or other) patients who require tube placement or pH monitoring for clinical management

not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Study 4: Efficacy and Safety Study in Pediatric Patients 1 To 11 Months of Age

Inclusion criteria: To be included in this study, infants will (a) be patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

The method by which the clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD is made will be recorded and summarized for each patient. These summaries will include the clinical history and results of laboratory tests used to establish the diagnosis (e.g., pH probe, gastroesophageal endoscopy, radionuclide milk study). Results from such laboratory tests will be provided regardless of whether they supported the final clinical diagnosis or not.

Design: This will be a multicenter, treatment-withdrawal study of the efficacy and safety of [*INSERT DRUG NAME*] in which treatment withdrawal is randomized, double-blind, and placebo controlled. The dosage(s) of [*INSERT DRUG NAME*] used in this study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 3, and as suggested by the results of other studies (e.g., literature studies of pediatric patients). The number of patients per treatment group required to complete the study is described in the Statistical Information section. Independent data review committees (e.g., for safety, efficacy, or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Run-in phase: All patients will receive [*INSERT DRUG NAME*] in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by [*INSERT DRUG NAME*] is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this part of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

Withdrawal phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of [*INSERT DRUG NAME*] or to receive matching placebo. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes.

Following randomization, patients will be followed closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

Study 5: Pharmacokinetic, Exposure/Response, and Safety Study in Pediatric Patients 1 To 11 Years of Age

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of [*INSERT DRUG NAME*]. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of [*INSERT DRUG NAME*]. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Exposure/Response Component:

This will be a randomized, double blind, dose-ranging study of [*INSERT DRUG NAME*]. The dosages of [*INSERT DRUG NAME]* used in this study will be selected as dosages likely to be therapeutically effective and safe, based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Eligible patients will be randomized in approximately equal proportions to one of at least three dose levels of *[INSERT DRUG NAME]*. After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 40 patients 1 to 5 years of age and 40 patients 6 to 11 years of age will complete at least 8 weeks treatment.

Study 6: Pharmacokinetic and Safety Study in Pediatric Patients 12 to 16 Years of Age

Inclusion criteria: To be included in this study, patients will (a) be 12 to 16 years of age inclusive, and (b) have a clinical diagnosis of suspected GERD, symptomatic GERD or endoscopically proven GERD. Endoscopy is not required for study entry or participation. Patients of both sexes will be enrolled in the single- and repeated-dose components of the study as well as in the eight-week safety component.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of *[INSERT DRUG NAME]*. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK

approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of *[INSERT DRUG NAME]*. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Eight-week Safety Component:

This will be a multicenter safety study of *[INSERT DRUG NAME]*. An open-label, non-randomized design is acceptable. Dosages of *[INSERT DRUG NAME]* used in this study will be selected as dosages likely to be therapeutically effective and safe based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Patients will be treated for at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 100 patients will complete at least eight weeks of treatment.

Indication to be Studied:

Treatment of gastroesophageal reflux disease (GERD)

Objectives and Rationale:

Studies 1 and 3:
(a) To characterize the pharmacokinetic/pharmacodynamic profile of single and repeated doses of *[INSERT DRUG NAME]* and to compare these profiles with those in adults and older pediatric patients.
(b) To collect information on the safety of single and repeated doses of *[INSERT DRUG NAME]*.

Study 2:
(a) To obtain efficacy data as measured by obstructive apnea for *[INSERT DRUG NAME]* in preterm infants and neonates.
(b) To assess the safety of *[INSERT DRUG NAME]* in preterm infants and neonates.

Study 4:
(a) To obtain efficacy data for *[INSERT DRUG NAME]* in pediatric patients 1 to 11 months of age.
(b) To assess the safety of *[INSERT DRUG NAME]* in pediatric patients 1 to 11 months of age.

Study 5:
(a) To characterize the pharmacokinetic profile of single and repeated doses of *[INSERT DRUG NAME]* in patients 1 to 11 years of age.
(b) To compare the safety and clinical outcome of pediatric patients 1 to 11 years of age with endoscopically proven GERD across different dosages of *[INSERT DRUG NAME]*.

(c) To determine the proportion of patients showing endoscopic evidence of healing after completion of therapy across different dosages of *[INSERT DRUG NAME]* in those pediatric patients 1 to 11 years of age who undergo follow-up endoscopy after treatment.

Study 6:
(a) To characterize the pharmacokinetic profile of single and repeated doses of *[INSERT DRUG NAME]* in patients 12 to 16 years of age.
(b) To collect information on the safety of single and repeated doses of *[INSERT DRUG NAME]* in pediatric patients 12 to 16 years of age.

Study Evaluations and Endpoints:

Pharmacokinetics: In the PK studies, appropriate pharmacokinetic parameters will be assessed for both the single- and repeated-dose portions of the studies (e.g., AUC, apparent clearance, T_{max}, $T_{1/2}$, apparent volume of distribution, C_{max}, and others as appropriate).

Pharmacodynamics: In the PD studies, appropriate pharmacodynamic parameters will be assessed (e.g., AUC of the gastric H+ concentration over time, intraesophageal pH, gastric pH, percentage of time gastric pH>4, and percentage of time gastric pH>3). Pharmacodynamic assessments will be made just prior to dosing and at appropriate intervals after dosing to encompass the duration of drug effect. For patients receiving repeated doses, pharmacodynamic assessments will be made at baseline (i.e., before therapy) and after the final *[INSERT DRUG NAME]* dose.

Safety and tolerability: In each study, the evaluation of safety will include a physical examination and clinical laboratory assessment before treatment and, at a minimum, after completion of the pharmacokinetic, pharmacodynamic, or clinical-outcome assessments. Assessment of adverse events will occur throughout each patient's study participation. Patients will be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure will be documented fully, as will the use of any rescue medications. All patients will be followed at least 2 weeks after final administration of test medication. Patients enrolled in studies 2 and 4 will undergo follow-up developmental, growth, and safety assessments 6 and 12 months after enrollment.

Other Clinical Outcomes and Endpoints:

Study 1: Apnea and bradycardia will be assessed concurrent to pHmetry.

Study 2: Respiratory signs and symptoms, including apnea and bradycardia, will be monitored. The primary outcome measure will be obstructive apnea assessed by repeat pneumogram(s) following patient enrollment.

Additional outcome parameters: patient discontinuations due to ineffective treatment, apnea as assessed by conventional cardio-respiratory monitoring and nursing observations, severity of apneic episodes (e.g., as manifested by drop in O_2 saturation, cyanosis, bradycardia and/or need for positive pressure ventilation).

Safety measures: overall mortality; adverse events including co-morbidities of prematurity (acquired sepsis/pneumonia, necrotizing enterocolitis, bronchopulmonary dysplasia); growth (weight, length, and head circumference); significant clinical laboratory changes, and trough blood levels determined in a subset of at least 24 patients.

Study 4: Supraesophageal and airway complications associated with GERD; GERD signs and symptoms (e.g., vomiting/regurgitation; irritability); growth parameters (including weight and height/length); frequency, severity, and duration of aspiration and wheezing; compliance.

Study 5: Signs and symptoms of pediatric GERD, concomitant antacid consumption, physical well-being.

Drug Information:

The studies described above should use an age-appropriate formulation of *[INSERT DRUG NAME]*. The relative bioavailability of these age-appropriate formulations should be determined and compared with the marketed formulation of *[INSERT DRUG NAME]*. Full study reports of any relative bioavailability studies should be submitted to the Agency. If age-appropriate formulations cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

Statistical Information:

In each pharmacokinetic study, the pharmacokinetic parameters of *[INSERT DRUG NAME]* may be summarized using descriptive statistics. In each pharmacodynamic study, the pharmacodynamic analysis will include an assessment of the time course of change of intragastric or intraesophageal pH, along with an assessment of dose effects. Mean ($\pm$SD) and median AUC for hydrogen ion secretion over the evaluation period will be calculated and compared among the doses.

In Study 2, treatment regimens will be compared with regard to change in obstructive apnea using appropriate statistical methods. A sufficient number of patients will complete the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided p#0.05).

In Study 4, treatment regimens will be compared with regard to clinical outcomes using appropriate statistical methods. A sufficient number of patients will complete the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided p#0.05).

In Studies 2, 4, and 5 treatment regimens will be compared with regard to change in growth parameters, symptoms and other responses.

Additional Information Needed:

Perform a thorough review of the medical literature on the use of *[INSERT DRUG NAME]* in pediatric patients and provide a critical analysis and summary.

In addition, you should address the use of *[INSERT DRUG NAME]* for the maintenance of healing of erosive esophagitis and *H. pylori* eradication in pediatric patients. This can be done by: 1) reviewing, assessing, and submitting the available published information on the use of *[INSERT DRUG NAME]* in these patient populations and considering whether for the pediatric population or any portion of the

pediatric population the disease and drug effects in those pediatric patients are similar as in adults or 2) a prospectively designed randomized, controlled clinical trial in this/these indication(s).

The Agency is concerned that pediatric patients may show progression of cellular changes beyond the proliferative changes in enterochromaffin-like (ECL) cells observed in adults who have used *[INSERT DRUG NAME]*. Before initiating the above clinical studies, please provide nonclinical and clinical data that helps to determine whether pediatric patients are at any increased risk with respect to these proliferative changes in gastric ECL cells.

To further assess the carcinogenicity potential of *[INSERT DRUG NAME]* and its safety for human use, perform a 26-week carcinogenicity study heterozygous p53 (+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose ranging study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints.

Before pediatric studies are initiated, you must document that pediatric patients are not at increased risk due to the carcinogenicity potential of *[INSERT DRUG NAME]*. Also, the Agency must have reviewed the submitted data and concurred with that assessment. We are available to discuss your plan for providing the requested data and studies that will be conducted.

Labeling That May Result From the Studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of Reports to be Submitted:

Full study reports (not previously submitted) should be submitted to the Agency addressing the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Specifically, the categories should include American Indian/Alaska Native, Asian/Pacific Islander, Black, White and Hispanic.

Timeframe for Submitting Reports of the Studies:

Reports of the above studies must be submitted to the Agency on or before [*INSERT DATE*].
Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission**, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED**

WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must be clearly **marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call [*INSERT NAME & TITLE]*, Regulatory Health Project Manager, at [*INSERT TELEPHONE NUMBER]*.
Sincerely,

[*INSERT NAME]*
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment

1. Pediatric patients 12 to 16 years of age, inclusive

The Written Request asks for a pharmacokinetic and safety study in this age group (Study 6). The course of GERD in this age group is similar to that in adults. Moreover, the effects of the proton-pump inhibitor, both beneficial and adverse, are expected to be similar in this pediatric age group and adults. Therefore, approval for pediatric use in this age group can be based on adequate and well-controlled studies in adults, with additional information supporting pediatric use (i.e., the pharmacokinetic and safety information requested in Study 6).

2. Pediatric patients 1 to 11 years of age, inclusive

The Written Request asks for a pharmacokinetic, exposure/response, and safety study in this age group (Study 5). As in pediatric patients 12 to 16 years of age, approval for pediatric use in this age group can be based on adequate and well-controlled studies in adults, with additional information supporting pediatric use. In this age group, however, the additional information supporting pediatric use includes not only pharmacokinetic and safety information, but also an exposure/response study. The exposure/response study is intended to provide some information on the effects of different doses of the proton-pump inhibitor on clinical outcomes in this age group.

3. Pediatric patients 1 to 11 months of age, inclusive

The Written requests asks for two types of studies in this age group: a) a pharmacokinetic, pharmacodynamic, and safety study (Study 3), and; b) an efficacy and safety study (Study 4). The course of pathological gastroesophageal reflux in this age group is not sufficiently similar to the course of GERD in adults to permit extrapolation of adult efficacy data. For example, manifestations of GERD in this age group often involve the respiratory tract or are supraesophageal, whereas in adults manifestations of GERD typically involve the upper gastrointestinal tract. In addition, the effects of the proton-pump inhibitor, both beneficial and adverse, may also be different in patients in this age group and in adults.

Therefore, in addition to pharmacokinetic, pharmacodynamic, and safety data, the Written Request asks for an efficacy study of a randomized withdrawal design. A randomized withdrawal design can minimize prolonged exposure to placebo in situations where that is felt to be undesirable or unfeasible. In addition, the Written Request has provisions for prompt discontinuation from randomized study therapy when discontinuation is felt to be clinically appropriate.

4. Neonates and preterm infants with a corrected age of less than 44 weeks

The Written Request asks for two types of studies in this age group: a) a pharmacokinetic, pharmacodynamic, and safety study (Study 1), and; b) an efficacy and safety study (Study 2). As in pediatric patients 1 to 11 months of age, adult efficacy data can not be extrapolated to this age group. Therefore, in addition to pharmacokinetic, pharmacodynamic, and safety information, the Written Request asks for an efficacy study of a randomized withdrawal design. As noted above, a randomized withdrawal design can minimize prolonged exposure to placebo in situations where that is felt to be undesirable or unfeasible. In addition, the Written Request has provisions for prompt discontinuation from randomized study therapy when discontinuation is felt to be clinically appropriate.